Drug Delivery

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Externally Triggered Glass Transition Switch for Localized On-Demand Drug Delivery**

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Controlled release of drugs from polymeric implants has been studied extensively, and has mainly focused on achieving zero-order release in time.[1–3] However, many therapeutic applications do not require constant drug release, or in the case of habituation or resistance to medication, even benefit from pulsatile administration, such as post-surgical pain control and the treatment of infections.[4–6] By non-invasive external triggering[7–14] of drug release from an implant, localized pulsewise administration can be realized according to the patient's needs, thus allowing for lower doses of potent drugs and thereby reducing the toxic side effects commonly associated with systemic administration. Controlling the precise level and location of a drug in the human body can thus greatly improve drug safety and efficacy.[15]

External regulation of on-demand drug release has been reported using a number of different stimuli.[6] Release based on polymer degradation or dissolution has been induced by ultrasound[7,8] and electrical triggering,[9,10] but these mechanisms prohibit long-term applications. Electrochemical[11] or electrothermal activation[12] has been applied for drug delivery from multireservoir microchips that require complex multistep lithographic fabrication. Alternatively, thermal triggers can be used for non-destructive on–off switching of drug release based on the lower critical solution temperature (LCST).[16,17] Oscillating magnetic fields,[18] near-infrared radiation,[13,19] and a radiofrequency field[20] have been used for non-invasive thermal triggering. However, the attained on–off ratios using the LCST transition are limited to values in the order of 70, and the relatively high leakage in the off-state reduces the effective lifetime of the implant.[13,14,19,21,22]

Herein we show that the large variation in diffusivity occurring near the glass transition temperature T_g of a polymer[23] can be used to activate drug release by thermal triggering. To demonstrate the effect of temperature on the release of ibuprofen near the T_g of poly(D,L-lactic acid) (PLDL; T_g midpoint = 56 °C, T_g trajectory = 50–60 °C, FDA-approved polymer), we placed compounded strands of polymer oversaturated with ibuprofen in a water bath at 37 °C. Transferring the strands into a bath at 55 °C resulted in a stepwise release of ibuprofen with an on–off ratio of about 400 (Figure 1a). During the 15-minute release pulses, the amount of ibuprofen liberated was very reproducible ((60.9 ± 12.6) μg from an implant initially consisting of about 60 mg of ibuprofen and about 90 mg of polymer), which can be attributed to oversaturation of ibuprofen. This oversaturation ensures replenishment of released ibuprofen by partial dissolution of the drug crystals, thus providing a constant concentration of ibuprofen dissolved in the polymer and, consequently, a constant driving force for release (Figure 2). Although the large plasticizing effect of ibuprofen decreases the T_g of the polymer to about 0 °C, no significant release is found at 37 °C, which can be attributed to the self-sealing property of the system. As the diffusion coefficient of ibuprofen outside the strand ($D \approx 10^{-9}\ m^2 s^{-1}$) is much higher than inside the polymer ($D < 10^{-12}\ m^2 s^{-1}$), the ibuprofen surface concentration is close to zero, resulting in a concentration gradient in the surface layer of the polymer strand (see the Supporting Information). This gradient causes a T_g profile, with the highest T_g located at the polymer/water interface. Therefore, although the bulk polymer is in the rubbery state, the outer surface of the polymer is in a glassy state, providing a switching layer (Figure 2), which based on diffusion theory is in the order of 10 μm (see the Supporting Information). This self-sealing mechanism accounts for the extremely low release in the off-state and, in addition, provides an intrinsic safety precaution, as rupture of the implant will not result in dose dumping. Drug release is thus controlled by changing the temperature of this switching layer around T_g. The generality of this concept was investigated by varying both the polymer matrix and the released drug. The use of poly(butyl methacrylate-*stat*-methyl methacrylate) (PBMA-MMA; M_w = 150 kDa; T_g midpoint = 46 °C) as polymer matrix containing 40 wt % ibuprofen resulted in on/off-

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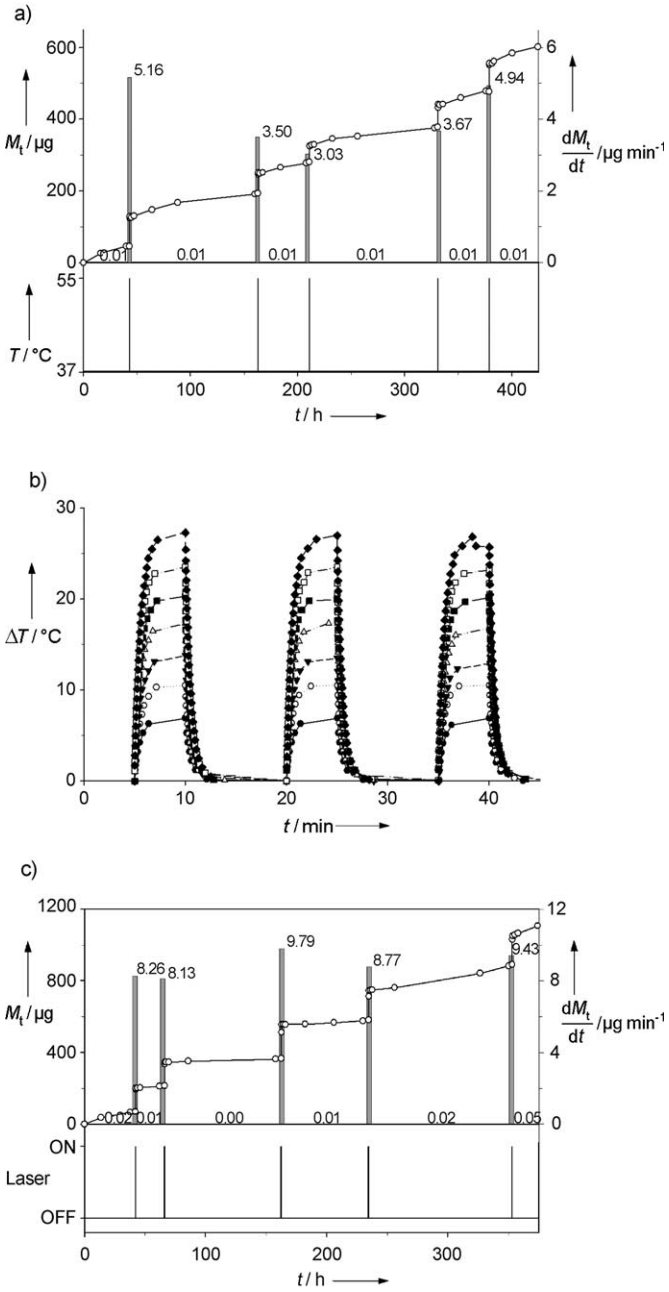

Figure 1. On-demand drug release from a polymeric matrix using NIR as external trigger. a) Repeated on-off switching of a PLDL strand (weight ≈ 150 mg) containing ibuprofen crystals in phosphate-buffered saline (PBS) by transferring the strand from a 37 °C to a 55 °C water bath. b) Surface temperature increase (ΔT) of a PLDL strand dip-coated with dye-doped PLDL ([QBDC]: 6000 ppm) at different laser powers (● 200 mW, ○ 270 mW, ▼ 350 mW, △ 450 mW, ■ 550 mW, □ 650 mW, and ◆ 750 mW). c) Repeated on–off switching of a PLDL strand oversaturated with ibuprofen and dip-coated with dye-doped PLDL ([QBDC]: 15 000 ppm) in PBS (T = 37 °C) induced by NIR laser at a power of 750 mW. In (a) and (c), circles represent cumulative release M_t, and bars indicate the average release rate dM_t/dt in a certain time interval. Each on-switch lasts 15 min.

ratios of circa 30, thus demonstrating the generality of the presented concept (see the Supporting Information). A higher off-release with PBMA-MMA as polymer matrix

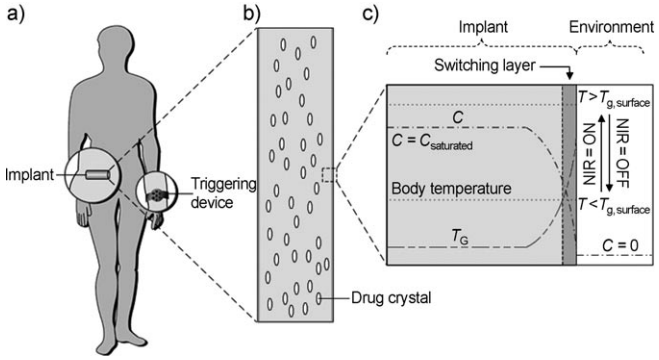

Figure 2. Overview of the glass transition switch. a) Drug release from a subdermal implant can be remotely switched on using a "watch-type" triggering device. b) The crystals in the implant ensure a constant saturated concentration of dissolved drug. c) The surface of the implant is glassy owing to the concentration profile in the switching layer, making the implant "self-sealing". T_g = glass transition temperature, C = drug concentration.

causes the lower on–off ratios compared to PLDL. The exact nature of the different behavior of the PBMA-MMA and PLDL is not yet understood, but is most likely related to drug solubility, polymer–drug interactions and/or differences in polymer free volume, which are all affected by ibuprofen loading.[24] The in vitro release of vanillin from PLDL was also investigated revealing on-off ratios of about 50 upon switching from 37 °C to 55 °C (see the Supporting Information). Decreasing the off-temperature to 25 °C strongly increased the on/off-ratio to over 1000, indicating the broader applicability of the reported concept.

To remotely induce the required temperature change, near-infrared radiation (NIR) was applied as external trigger. The minimum in absorption of blood and tissue material around 780 nm allows a significant penetration depth of NIR in tissue.[25,26] This wavelength can effectively be transformed into heat by a quaterrylenebis(dicarboximide) derivative acting as a dye with a high quantum yield of thermal relaxation.[27] This dye is reported to be non-toxic, thus permitting safe application in biomedical devices.[28] To ensure sufficient heating by NIR, the implant was dip-coated with a layer of PLDL containing the dye. The glass transition temperature of the polymer coating is hardly influenced by addition of the dye at these low concentrations (in the range of 1 % w/w). Figure 1b displays heating of coated PLDL rods, clearly demonstrating a rapid increase in surface temperature with initial heating rates up to 2 °C s^{-1}. In this system, steady-state surface temperatures are attained within 1–2 min. The heating rate and the increase in temperature can be controlled by the NIR intensity applied. The use of NIR for repeated in vitro ibuprofen release from PLDL implants is demonstrated in Figure 1c. The off-situation is characterized by a very low release rate (< 0.01 µg min^{-1}), whereas high release rates of approximately 8–10 µg min^{-1} are obtained in the on-state, leading to on–off ratios of more than 1000. Reproducibility tests, in which three separate implants were triggered twice, revealed a relative standard deviation of 18 % for the amount of ibuprofen released in 15 min.

The potential of this drug delivery concept was further explored by performing in vivo experiments with male Sprague–Dawley rats (Figure 3). To avoid the surrounding tissue from being exposed to excessive temperatures

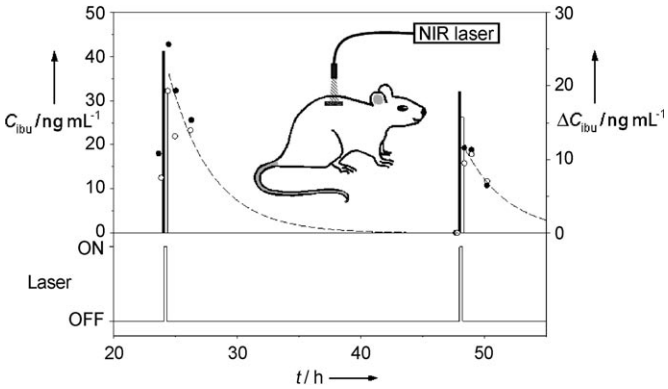

Figure 3. NIR-induced in vivo release from PLDL strands oversaturated with ibuprofen and dip-coated with dye-doped PLDL ([QBDC]: 6000 ppm) implanted subdermally in the back of male Sprague–Dawley rats (Rat A: ●, Rat B: ○) at a laser power of 750 mW. Circles represent ibuprofen concentration C_{ibu} in the blood plasma, bars indicate increase in ibuprofen concentration ΔC_{ibu} during NIR irradiation. Each irradiation lasts 15 min. Curves serve to guide the eye. The dye concentration differs from the in vitro experiments described in Figure 1c, as further optimization of the in vitro experiments were performed during the long approval procedure for the in vivo experiments.

(>43 °C), the polymer strand was tightly wrapped in a biopsy bag that is permeable for diffusing species, resulting in a total implant diameter of 3–4 mm. The stagnant film of bodily fluid in the biopsy bag seems to provide effective insulation, as visual tissue inspection following removal of the implant after the in vivo release experiments revealed no tissue damage. The significant increase in systemic ibuprofen concentration upon NIR irradiation clearly illustrates successful in vivo release based on the glass transition switch. When the trigger is turned off, the level of ibuprofen in the blood plasma decreases rapidly owing to drug metabolism. The increase in systemic ibuprofen concentration ((19.8 ± 3.2) ng mL^{-1}) was similar during both cycles of on-demand release in the two rats. Because of the somewhat complex pharmacokinetics of ibuprofen that arise from storage in tissue followed by slow release and degradation, it is not possible to calculate exact release rates from these experiments, making comparison with the in vitro experiments less straightforward. The presence of ibuprofen in the blood plasma before the first cycle is presumably caused by residual ibuprofen on the surface of the implant.

NIR is especially effective for triggering drug release from implants located at depths up to several centimeters.[25] For higher penetration depths, scattering by tissue in this wavelength region limits the use of NIR. Therefore, we have performed explorative experiments similar to those described above in which the applicability of alternative external temperature triggers was demonstrated. On-demand drug delivery was induced using therapeutic ultrasound (1–3 MHz), which is suitable for soft tissue applications owing to the difference in attenuation between water/tissue and the polymer (see the Supporting Information). Drug release was also triggered using an alternating magnetic field to heat polymer strands containing superparamagnetic iron oxide nanoparticles (see the Supporting Information). Magnetism is especially promising, as it allows triggering inside the entire human body. The use of various triggers underlines the versatility of this T_g-based switching mechanism for pulsatile drug release.

To conclude, we have demonstrated repeated and reproducible on/off drug release by non-invasive selective heating of the implant using near-infrared radiation (NIR), both during in vitro and in vivo experiments, attaining on–off ratios in excess of 1000. Release of ibuprofen below T_g was extremely low, and was attributed to the spontaneous formation of a glassy surface layer, whereas in the rubbery state ($T > T_g$) ibuprofen readily diffused out of the implant. The concept presented herein permits long-term and patient-friendly administration of a wide variety of medicines, ranging from systemic dosing of drugs with low oral bioavailability to drugs required locally. It should be mentioned that the use of PLDL might limit long-term applications owing to its biodegradability. Therefore, current research efforts are focusing on the development of alternative non-biodegradable polymer that have sufficient low off-release at 37 °C. We believe that the presented concept has a broad application possibility using different polymer matrices in combination with a variety of plasticizing drugs.

Potential applications of the reported on-demand drug delivery concept are envisioned for patients suffering from a chronic pain disorder or recurring inflammations, such as rheumatoid arthritis, and these patients would benefit from dosing at will. Cell damage caused by relatively potent drugs during chemotherapy could be suppressed by localized on-demand administration.[29] Patients known to be at risk of acute and lethal conditions could instantly provide the required antidote, such as antihistamines in the case of anaphylactic shock. We anticipate that the results described herein can lead to the development of new clinical treatment systems and enable patient-controlled self-administration.

Experimental Section

Strands of poly(D,L-lactic acid) (PLDL, $M_w = 460$ kDa relative to PS standard, amorphous copolymer of 70% L-lactide and 30% D,L-lactide, Purac) oversaturated with 40 wt% ibuprofen (Genfarma) were prepared in a custom-built twin-screw minicompounder (capacity: 5 g, $T_{set} = 165$ °C). Strands of PBMA-MMA ($M_w =$ 150 kDa, Sigma–Aldrich) were prepared in a similar manner. Compounded strands (diameter ca. 2 mm, length ca. 20 mm, weight ca. 100 mg) were coated with a quaterrylenebis(dicarboximide) derivative (QBDC, BASF) by dip-coating twice in a 4.5% w/w solution of PLDL in tetrahydrofuran (Biosolve) containing QBDC.

The increase in surface temperature of a QBDC-coated polymer strand when irradiated by NIR was measured using a non-contact infrared sensor (SP I-TEC 2060, Sensor partners B.V.). The sensor was fixed in an XYZ translator (PT3, Thorlabs GmbH) to allow exact positioning of the sensor relative to the sample.

In vitro temperature induced release studies were performed by transferring a screw-cap jar containing a PLDL strand in 50 mL

phosphate buffered saline (PBS, pH 7.4, Sigma) from a 37 °C to a 55 °C water bath (Grant OLS 200). In vitro NIR-induced release studies of a PLDL strand were performed in a custom-made 54 mL jacketed glass vessel ($T = 37$ °C) completely filled with PBS and sealed with a glass cover. The fiber-coupled CW-laser diode module (HPM (Power Technology, Inc.), $\lambda = 785$ nm, N.A. = 0.22) was fixed 16 mm above the PLDL strand. All in vitro samples (500 μL) were analyzed by HPLC (C18 Discovery HS 150 × 4.6 mm–3 μm, 50/50 % v/v acetonitrile/water (with 0.1 % v/v TFA), flow = 1.2 mL min^{-1}, UV detection at 223 nm). Fresh PBS solution was added to maintain a constant system volume.

For the in vivo study, a PLDL strand was tightly wrapped in a tissue specimen bag (Shandon) and implanted subdermally in male Sprague–Dawley rats (280–300 g). The laser was kept at the same distance (14 mm) from the skin of the lightly anaesthetized rat (isofluorane inhalation; 2 % at 250 mL min^{-1}) throughout NIR irradiation. Blood plasma samples (200 μL) were taken at predefined intervals from a hind leg of the rats. Samples were centrifuged (3000 rpm, 20 min) and analyzed by LC-MS/MS (Xterra C18, 50 × 2.1 mm–3.5 μm, turbo ion spray (ESI) negative-ion-mode mass detection). The protocol was approved by the Ethics Committee on Animal Experiments of the University of Maastricht (DEC protocol #2006–066).

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